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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
CUNNINGHAM, T	
ART UNIT	**PAPER NUMBER**
1816	

DATE MAILED: 12/18/97

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/452,843	Applicant(s) Sette et al.
	Examiner Thomas Cunningham	Group Art Unit 1816

☒ Responsive to communication(s) filed on *10/14/97*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-3* is/are pending in the application.

Of the above, claim(s) *2* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1 and 3* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *9*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. Claims 1 and 3 are active. Claim 2 is withdrawn because none of the recited peptides contain the elected submotif: Xaa Pro Xaa Xaa Xaa Xaa Xaa Xaa Met.

2. Applicant's election with traverse of Group I, claims encompassing the peptides having the motif: Xaa Pro Xaa Xaa Xaa Xaa Xaa Xaa Met, in Paper No. 11 is acknowledged. The traversal is on the ground(s) that such a restriction is a violation of the PTO rules and case law precedent. This is not found persuasive for the following reasons:

A. Applicant urges on page 4 of the response that restriction is discretionary and should not be imposed if no undue burden is imposed on the Examiner. Applicant urges that the Examiner must show that examination of the claims would involve substantially different prior art searches. A different field of search is required for each of the recited motifs. Search of each of the structurally distinct motifs results in identification of materially different prior art proteins containing the different motifs. Thus, twenty different amino acid sequence searches would have to be performed and evaluated in order to examine the twenty recited motifs. Surely the Applicant would agree that if

twenty different structurally unrelated proteins were being claimed in a single claim, restriction amongst the different proteins would be proper. The situation here is similar, each motif requires a separate amino acid sequence search and application of materially different prior art references.

B. Applicant has had the opportunity to have nonelected binding motifs examined by admitting that the motifs are obvious over each other, and that the prior art applicable to one would also apply under 35 U.S.C. 103(a) to the other binding motifs. Applicant has not made this admission and has admitted on page 4 of the election that the different binding motifs are "separately patentable. Therefore, it is presumed that Applicant agrees that each of the peptide binding motifs requires a separate prior art search. Applicant's failure to do this is taken as an admission that each of the binding motifs is patentably distinct and involves a separate prior art search.

C. Applicant may not be aware of the examination burden imposed on the Examiner to examine all the recited binding motifs, however, an undue burden is placed on the Examiner in the examination of more than one binding motif. As a practical

matter, the Examiner is allocated only about 20 hours per round of prosecution. This 20 hrs includes search time, analysis of prior art, interviews with Applicant and administrative tasks, and writing at least two office actions. Proper searching and evaluation of twenty separate sets of prior art for each of the twenty different binding motifs would greatly exceed the amount of time allocated for examination and thus impose an administrative burden on the Examiner or result in an incomplete examination of the claimed subject matter. Use of an election of species requirement instead of a restriction requirement would probably result in the Applicant limiting the broad binding motif of claim 1 to avoid the cited prior art, and necessitate a new search of a second, materially different binding motif, thus at least doubling the examination time required. This in unlike a situation where different chemical species sharing a common structural nucleus are being examined. In such a case examination of the elected species results in examination of the common structural nucleus of the class of compounds being claimed which also pertains to examination of the nonelected species.

D. Applicant's cited case law has been reviewed by not on point. It is noted that unlike Weber, Soder and Boksay, 198 USPQ 328

(CCPA 1978), no rejection of claims as being "improper Markush claims" is at issue. The court lacks jurisdiction over restriction requirements that do not involve rejection of claims. Therefore, case law precedent is not relevant to the restriction requirement.

E. The Applicant is invited to contact the Examiner to discuss whether additional subject matter may be examined along with the elected invention without imposing an undue burden on the Examiner.

Therefore for the reasons previously stated in the original restriction requirement and above, the requirement is still deemed proper and is therefore made FINAL.

3. Claims 1 and 3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claims 1 and 3 it is unclear what the metes and bounds of the word "peptide" are? Is this limited to amino acid sequences

100 residues or less? Is this term functionally limited to only those peptides that are of the appropriate size to bind to both a Class I and class II molecule, e.g. 9-10 amino acid residues long? Is the language of claim 1 intended to be limited to peptides that consist of nine or ten amino acid residues?

B. In claims 1 and 3 it is unclear what the meaning of the word "composition is". Is this term limited to noncovalently-associated ingredients, e.g. a peptide in saline solution? Does it encompass covalently associated components such as a fusion protein comprising the recited peptide? Does it encompass peptides noncovalently bound to MHC molecules?

C. In claim 1 it is unclear how many residues are encompassed by the term "about". How can a peptide have "between about 9-10 residues"--doesn't either have 9 or 10 residues?

D. In claims 1 and 3 it is unclear what the term "immunogenic peptide" refers to. Is this limited to peptides which are recognized by T cells when presented by an MHC molecule? Does this term require that the peptide be capable of inducing an antibody response?

E. Claim 2 (nonelected) would more distinctly claim the invention if it recited "selected from the group consisting of the group of peptides with SEQ ID NO's 1-21". Claim 2 also contains a spelling error: "immunogneic peptode".

F. Claim 3 lacks antecedent basis in independent claim 1 which is directed to a composition, not a peptide.

G. The term "therapeutically effective dose" as used in claim 3 is vague and indefinite because it is unclear what type of therapy is being referred to. Functional terms are acceptable if the function is definite. E.g. is the dose effective for treatment of T cell mediated diseases, a particular autoimmune disease, HIV infection, etc?

H. In the absence of further comment by the Applicant the term "HLA molecule" as used in claim 1 has been interpreted as embracing human MHC Class I or Class II molecules and excluding other types of histocompatibility molecules, e.g. non-human Class I or II molecules, minor histocompatibility molecules, complement components and other antigen-presenting molecules like CD1.

4. Claims 1 and 3 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant claims as directed to the elected species encompass compositions comprising at least $(20)^7$ = 1,280,000,000 different peptides.

A. One with skill in the art is not enabled to use the claimed peptide compositions or methods because the specification does not provide adequate evidence of which of over 1,280,000,000 peptides would be capable of binding to more than one HLA molecule.

Claim 1 recites this limitation in functional form, but does not specify which structural characteristics are critical for a peptide to bind to more than one HLA molecule, other than specifying that the peptide must have 8-11 residues, and have particular amino acid residues in the penultimate N-terminal residue, and at the C-terminal residue.

One with skill in the art would not be able to predict which peptides falling within these parameters would be capable of binding to more than one HLA molecule, because substitution of the other unspecified peptide residues with different amino acids

would be expected to perturb the ability of the peptides to bind to HLA molecules, e.g. the presence of the binding motif in necessary but not sufficient to ensure binding to HLA.

B. Second, one with skill in the art is given no guidance as to the structures of peptides falling within the recited parameters would be expected to contain residues capable of stimulating T cells (T cell epitopes). Thus, even were one able to predict which peptides would bind to more than a single type of HLA protein, it would require undue experimentation to determine which amino acid substitutions would yield peptides that could be used to stimulate T cell responses. The presence of the agretope (portion of the peptide that binds to HLA (or MHC) molecule alone is insufficient, because activation of T cells requires the presence of both an agretope and epitope so that a ternary complex of peptide, HLA (or MHC) antigen, and T cell receptor may be formed.

C. Assuming <u>arguendo</u> that one with skill in the art would obtain a peptide with a agretope that binds to more than one type of HLA molecule and T cell epitope capable of stimulating a T cell (CTL response) it would be unpredictable whether one with skill in the

art could use said CTL response to treat disease. For instance, one with skill in the art would not expect that a CTL response against a determinant from human immunodeficiency virus (HIV) would prevent AIDS.

D. One with skill in the art would not expect that the claimed "immunogenic" peptides would be immunogenic outside the context of an MHC molecule binding pocket. The claims do not recite this critical limitation on immunogenicity. T cell recognition of these short peptides would be expected to require association of an MHC (or HLA) molecule to form a ternary complex. B cell recognition of these peptides would be expected to require conjugation of these short peptides to a carrier moiety.

In re Fisher, 426 F.2d 833, 166 USPQ 18 (CCPA, 1970) indicates that the more unpredictable an area is, the more specific enablement is required in order to satisfy 35 U.S.C. 112, first paragraph. In the instant case, it is unpredictable which substitutions of the unspecified amino acid residues would yield peptides that could be used by one with skill in the art therapeutically or diagnostically. This unpredictability is known in the art as evidence by Rudinger who indicates that "The

significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted a priori, but must be determined from case to case by painstaking experimental study".

The identity of the unspecified amino acid residues (and thus the identity of the T cell epitope of the recited peptides) is defined in functional terms. Functional definition of a product is not per se fatal if the structure is conventional or can be determined without undue experimentation, In re Gunn, 190 USPQ 402 (CCPA 1976, In re Donohue, 193 USPQ 136 (CCPA 1977). The breadth of the claims as well as predictability are important factor in determining whether undue experimentation would be required to practice an invention, Ex parte Forman, 230 USPQ 546 (BPAI 1986). In the instant case there are more than 20^9 different peptides that meet the structural limitations of the instant claims and the amino acid structure of the T cell epitopes formed by the unspecified amino acid residues is unpredictable without experimentation on a peptide-by-peptide basis. Therefore, undue experimentation would be required to determine which substitutions of the unspecified amino acid residues would yield peptides usable by one with skill in the art.

E. One with skill in the art would not expect to be able to use the peptides of SEQ ID No's 1-21 as they fall within the elected species for any useful therapeutic of diagnostic purpose. It would be unpredictable whether these peptides would be capable of binding to, and being recognized by T cells in a manner that would achieve a therapeutic effect, e.g. induce CTL responses against pathogen-infected cells.

For instance, in order for the peptides to induce therapeutically relevant cellular responses a subject's antigen presenting cells must naturally process and present similar pathogen-specific determinants during infection. E.g. the peptide of SEQ ID NO: 1 from HBV env could be administered to a patient and subsequently induce specific CTL responses to itself (in the context of the patient's MHC molecules). However, these specific CTL's would not necessarily recognize HBV-infected cells, UNLESS those cells also presented the SEQ ID NO:1 determinant.

F. One with skill in the art would not reasonably expect to use the claimed methods and compositions because pharmaceutical therapies are unpredictable for the following reasons:

(1) the peptide may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to inherently short half-life of the peptide or protein.

(2) the peptide may not reach the target area, i.e. the peptide may not be not be able to cross the mucosa or may be adsorbed by fluids, cells and tissues where the peptide(s) or protein has no effect.

(3) other functional properties, known or unknown, may make the peptides unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO BD. APP. & Inter. 1992).

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

6. Claim 1 is rejected under 35 U.S.C. § 102(b) as being by Bosisio et al., Gazz. Chim. Ital. 97(12):1848-57 (1967) or Fujii et al., Chem. Pharm. Bull. 31(12):4259-4262 (1983). This claim encompasses peptide compositions comprising 9 residue peptides with a "P" in position 2 and an "M in position 9.

Bosisio et al., see abstract, teach the peptide DPNKFIGLM. Fujii et al, page 4261 (middle of page) teach the KPDQFVGLM peptide. Both these peptides meet the recited structural limitation, i.e. they both contain the elected P/M motif. The claim language does not recite any other element of the claimed composition, so the prior art disclosure of the above two peptides meet the recited structural limitations of the claim.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas M. Cunningham, Ph.D, J.D. whose telephone number is (703) 308-3968. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

TC

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